al., PNAS 93, 12817, 1996). The FK506 portion of the hybrid molecule was synthesized as the N-hydroxysuccinamide activated ester from the natural product FK506 in a total of four synthetic modifications (Licitra, et al., PNAS 93, 12817, 1996). The dexamethasone amine (and FK506 activated ester) were coupled to aminosalicyclates as shown in FIG. 3. --

In the Claims

Please amend Claims 1, 6, 13, 14, 16, 17, 18, 26, 27 and 31, as follows:

1. A method for identifying a cellular component to which a small molecule is capable of binding, comprising:

(a) providing a hybrid ligand consisting essentially of two ligands, identified as ligand A and ligand B that are linked together, wherein

(i) ligand A has a specificity for a predetermined target;

(ii) ligand A forms an irreversible (covalent) bond with the predetermined target;

(iii) and ligand B is the small molecule;

(b) introducing the hybrid ligand into at least one sample, the sample containing an environment, the environment containing;

(i) a first expression vector, comprising DNA encoding the target for ligand A, linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(ii) a second expression vector comprising a random DNA fragment encoding a polypeptide linked to a second transcriptional module for expression as a second hybrid protein; and

(iii) a third vector comprising a reporter gene wherein the expression of the reporter gene is conditioned on the proximity of the first and second hybrid proteins;

(c) permitting the hybrid ligand to bind covalently the first hybrid protein through ligand A and the second hybrid protein through ligand B so as to activate the expression of the reporter gene;

(d) identifying those samples expressing the reporter gene; and

(e) characterizing the second hybrid protein in the samples identified in (d) so as to determine the cellular component to which the small molecule has a binding affinity.

6. A method according to claim 1, wherein the environment in step (b) is selected from the group consisting of insect cells, yeast cells, mammalian cell, and their lysates.

13. A method according to claim 1, wherein the second expression vector of step (b)(ii) contains a random DNA fragment of a size suited for encoding a gene product wherein said random DNA fragment is from a library of DNA.

14. A method according to claim 13, wherein the random DNA fragments in the library are selected from the group consisting of genomic DNA, cDNA and synthetic DNA.

16. A method according to claim 14, wherein the library is a cDNA library derived from an immune cell.

17. A method according to claim 16, wherein the cDNA is derived from an immune cell capable of producing an immune response to a small molecule contaminant.

18. A method according to claim 1, wherein the ligand A or B of step (a) is a mechanism-based irreversible enzyme inactivator.

26. A method according to claim 1, wherein the cellular component is a protein.

27. A method according to claim 24, wherein the steps (b) - (e) of the method are repeated using an expression vector encoding the second hybrid protein of step (e) and a hybrid ligand containing ligand A and ligand B in the presence of a preparation of random small molecules that bind competitively to the hybrid ligand and identifying the small molecule capable of competitively binding the target molecule for searching for new target molecules in an iterative process.

31. A kit for detecting interactions between pharmacologically relevant small molecules and proteins comprising;

(a) a preactivated ligand A and reagents for forming a hybrid ligand with at least one type of ligand B, wherein ligand A has a specificity for a predetermined target and forms an irreversible (covalent) bond with the predetermined target;

(b) a first expression vector comprising DNA encoding a target for ligand A linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(c) a second expression vector comprising a random DNA fragment encoding a polypeptide linked to a coding sequence for a second transcriptional module for expression as a second hybrid protein;

(d) a third vector comprising a reporter gene wherein transcription of the reporter gene is conditioned on the proximity of the first and second hybrid proteins;

(e) an environment for transcription and translation of the first and second hybrid proteins and reporter genes; and

(f) a means for detecting the expression of the reporter gene following the formation of a trimeric complex between the hybrid ligand and the first and second hybrid proteins.

Please add Claims 32-34 as follows:

--32. A method according to claim 1, wherein the ligand A or B of step (a) is an aminoalkyl salicylate.

33. A method according to claim 1, wherein the ligand A or B of step (a) is selected from the group consisting of clavulanate and sulbactam. — ? Support

34. The method according to claim 1, wherein the ligand A of step (a) is chosen from the group consisting of an affinity labeling agent, a mechanism based enzyme inactivator, a ligand for which a recombinant protein has high affinity, and a ligand which covalently labels the target upon being contacted with a biocatalyst.--